REMARKS

Claims 1 to 19, 22, 25, 41, 42, and 52 to 73 are pending in the application. Claims 1, 25, 42, and 53 have been amended, and claims 14, 15, 64, and 65 have been canceled, herein, without prejudice. No new claims have been added. Applicant respectfully requests entry of the amendments because they place the claims in better form for appeal. M.P.E.P. § 714.12. Applicant did not present the amendments earlier because Applicant believed that his reply to the previous Office action was sufficient to overcome all of the outstanding rejections and to place the claims in condition for allowance.

Applicant respectfully requests reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Lack of Enablement

Claims 1 to 19, 22, 25, 41, 42, and 52 to 73 have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Office Action asserts that the specification is enabling for methods of inhibiting the replication of Hepatitis C virus (HCV) serotypes 1b and 2a/2c in an individual infected with HCV, and having hepatocellular carcinoma (HCC) or cells that do not express argininosuccinate synthase (ASS) and are auxotrophic for arginine,[1] but does not enable methods of inhibiting HCV replication in an individual infected with HCV that does not suffer from HCC or does not have cells that do not express ASS and are auxotrophic for arginine. Applicant respectfully requests reconsideration and withdrawal of the rejection because the specification enables methods for inhibiting HCV replication in individuals infected with HCV that do not suffer from HCC.

Preliminarily, Applicant notes that claims 1, 25, 42, and 53 have been amended to recite methods of inhibiting the replication of HCV serotypes 1b and 2a/2c and methods of reducing the viral titer of HCV serotypes 1b and 2a/2c. Support for the amendments is found throughout the specification as originally filed. No new matter has been added.

When making an enablement rejection, the Examiner bears the initial burden of establishing a reasonable basis to question the enablement provided for the claimed subject matter. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). A specification that contains a

[1] Office Action dated January 26, 2006, page 9.

teaching of the manner and process of making and using an invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented ***must be taken as being in compliance with the enablement requirement*** unless there is a reason to doubt the objective truth of the statements contained therein. M.P.E.P. §2164.04. "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971). Acceptable support for an enablement rejection can take the form of ***specific findings of fact, supported by the evidence***. M.P.E.P. § 2164.04. "References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 24 (C.C.P.A. 1971). However, ***specific technical reasons are always required***." M.P.E.P. § 2164.04 (emphasis added).

The specification enables those skilled in the art to practice methods for inhibiting replication of HCV serotypes 1b and 2a/2c in individuals infected with HCV that do not suffer from HCC without undue experimentation, and the Office action has failed to provide a reasonable basis supported by evidence to question the enablement provided for the claimed subject matter. For example, examples 7 and 8 describe experiments demonstrating that arginine deiminase covalently bound to polyethylene glycol (ADI-PEG) inhibits the replication of HCV through a mechanism that does not involve or require HCC cells. Cultures of AVA5 cells (***heptoblasoma*** cells stably transfected with HCV)[2] were treated with various concentrations of ADI-PEG and the level of inhibition of viral replication that occurred in the absence of the killing of the host cells (the selectivity index) was determined.[3] As can be seen from the results presented in Example 8, ADI-PEG inhibits HCV from replicating in heptoblastoma host cells (***which are not HCC cells***) with a selectivity index of 12, indicating that the enzyme inhibits HCV replication through a mechanism that does not involve the killing of the heptoblastoma host cells. Example 8 thus demonstrates that ADI-PEG inhibits HCV replication ***in the absence of HCC cells*** through a mechanism that does not involve host cell killing.

[2] Paragraph 153 of the specification.
[3] A selectivity index greater than 10 indicates that viral replication is inhibited in the absence of host cell killing.

Moreover, as explained in the declaration pursuant to rule 132 of John S. Bomalaski submitted with the response to the official action issued April 22, 2005, the results of clinical trials conducted on behalf of Phoenix Pharmacologics indicate that a correlation does not exist between the response of HCC tumors to ADI-PEG and the response of HCV to ADI-PEG in patients infected with HCV and suffering from HCC. As explained in the response, in certain patients, ADI-PEG dramatically reduced HCV titer, but HCC tumors were stable or only modestly affected. Another patient made a complete recovery from HCC, but the patient's HCV titers only decreased modestly. The *in vivo* clinical trial data thus demonstrate that ***ADI-PEG inhibits HCV replication through a mechanism that does not involve the killing of HCC cells***. The Office has failed to provide acceptable evidence or reasoning as to why the truth or accuracy of these results should be doubted. The Office has presented no evidence or reasoning explaining how the HCV viral titer in a patient can decrease dramatically following treatment with ADI-PEG, while the patient's HCC tumors are not affected or are affected only modestly, if the killing of HCC cells is required for inhibition of HCV replication.

The Office action incorrectly asserts that "the specification does not provide any guidance or teachings showing that ADI-PEG is capable of inhibiting HCV replication in the absence of HCC cells,"[4] and further mistakenly asserts that "the presence of HCC cells is crucial to the operability of Applicant's claimed invention."[5] As discussed above, Example 8 demonstrates that ADI-PEG inhibits the replication of HCV in heptoblastoma cells, ***which are not HCC cells***, through a mechanism that does not involve the killing of the heptoblastoma cells. Accordingly, in contrast to the assertion made in the Office action, the specification demonstrates that ADI-PEG inhibits HCV replication in the absence of HCC cells, and the presence of HCC cells is ***not*** crucial to the operability of the claimed subject matter.

Finally, the Office action asserts that ADI-PEG "is not capable of inhibiting the replication of all HCV genotypes,"[6] but states that the specification does enable methods for

[4] Office Action dated January 26, 2006, page 4.
[5] *Id.* at 5.
[6] *Id.* at 4.

inhibiting HCV genotypes 1b and 2a/2c.[7] As discussed above, claims 1, 25, 42, and 53 have been amended to recite methods of inhibiting the replication of HCV serotypes 1b and 2a/2c and methods of reducing the viral titer of HCV serotypes 1b and 2a/2c. Because the specification demonstrates that ADI-PEG inhibits the replication of HCV serotypes 1b and 2a/2c in the absence of HCC cells, the specification enables the full scope of the subject matter recited in the amended claims. Applicant accordingly, respectfully requests withdrawal of the rejection.

Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully Submitted,

Date: April 17, 2006

Jane E. Inglese, Ph.D.
Registration No. 48,444

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

[7] *Id.* at 9.